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April 9, 2013

BY EMAIL AND REGULAR US MAIL

Bruce C. Tierney, M.D.
Captain, US Public Health Service
Agency for Toxic Substances and Disease Registry
Chamblee Campus, Bldg. 106, Room 5018
4770 Buford Highway NE, MS F-59
Atlanta, GA 30341

Re: Health Consultation – Exposure Investigation Report: Perfluorochemical Serum Sampling In the Vicinity of Decatur, Alabama – Morgan, Lawrence, and Limestone Counties (ATSDR, April 1, 2013)

Dear Dr. Tierney:

In our letter to you yesterday, it appears that the wrong publication was attached as Exhibit F. The correct version is attached hereto. We apologize for any confusion. Thank you.

Very truly yours,

Robert A. Bilott

RAB:mdm
Attachment

13433348.1

Occurrence and Potential Significance of Perfluorooctanoic Acid (PFOA) Detected in New Jersey Public Drinking Water Systems

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Received January 28, 2009. Revised manuscript received April 16, 2009. Accepted April 28, 2009.

After detection of perfluorooctanoic acid (PFOA) in two New Jersey (NJ) public water systems (PWS) at concentrations up to 0.19 μg/L, a study of PFOA in 23 other NJ PWS was conducted in 2006. PFOA was detected in 15 (65%) of the systems at concentrations ranging from 0.005 to 0.039 μg/L. To assess the significance of these data, the contribution of drinking water to human exposure to PFOA was evaluated, and a health-based drinking water concentration protective for lifetime exposure of 0.04 μg/L was developed through a risk assessment approach. Both the exposure assessment and the health-based drinking water concentrations are based on the previously reported 100:1 ratio between the concentration of PFOA in serum and drinking water in a community with highly contaminated drinking water. The applicability of this ratio to lower drinking water concentrations was confirmed using data on serum levels and water concentrations from other communities. The health-based concentration is based on toxicological end points identified by U.S. Environmental Protection Agency (USEPA) in its 2005 draft risk assessment. Recent information on PFOA's toxicity not considered in the USEPA risk assessment further supports the health-based concentration of 0.04 μg/L. In additional sampling of 18 PWS in 2007–2008, PFOA in most systems was below the health-based concentration. However, PFOA was detected above the health-based concentration in five systems, including one not previously sampled.

Introduction

Perfluorooctanoic acid (PFOA) is found in blood of people worldwide (*1*), including 99.7% of a representative sample of the U.S. population (*2*). In studies of U.S. populations, the geometric mean serum levels were 3.9 μg/L in 2003–2004 and 3.4 μg/L in 2006 (*2, 3*). This widespread human exposure is of concern due to PFOA's persistence and toxicity. PFOA has a half-life of several years in humans (*4*), and caused adverse effects on development, lipid metabolism, liver, and the immune system, and tumors in several organs in animals (*5*). In some studies, maternal exposures in the general population were associated with decreased birth weight and other measures of fetal growth (*6–8*), while other studies did not find these effects (*9, 10*). Some studies of exposed workers found associations with adverse outcomes including diabetes mellitus and increased cholesterol, whereas other studies were negative (*5*). Preliminary results of a study of almost 70 000 people exposed through drinking water suggest an association with several clinical parameters measured in blood, including increased cholesterol (*11, 12*).

Sources of exposure to PFOA include consumer products (*13*), house dust (*14*), diet (*15*), and drinking water (*16*). Exposure also occurs through metabolism and environmental transformation of the related chemical, 8:2 fluorotelomer alcohol, which is widely used in food packaging and other products (*17*).

PFOA and other perfluorinated chemicals were detected in surface waters (*18–23*) and drinking water (*20, 24, 25*) in several countries, and in groundwater contaminated by fire fighting foams (*26*). Drinking water has been contaminated by sources such as industrial facilities and landfills (*16, 27*), and by use of a contaminated soil conditioner on agricultural land (*20*). Blood levels of PFOA are elevated in communities with contaminated drinking water (*16, 20*), with the median serum concentration approximately 100-fold higher than in drinking water in those exposed for at least two years (*16*).

The first goal of this study was to evaluate the occurrence of PFOA in NJ public water systems (PWS), following its detection in groundwater of two PWS at concentrations from 0.007 to 0.19 μg/L (*28*). An occurrence study was conducted by NJDEP in 2006, and additional sampling was performed by NJ PWS in 2007–2008. The additional goals were to evaluate the significance of PFOA in drinking water for human exposure and potential human health risk. The contribution of drinking water concentrations such as those found in NJ to total exposure to PFOA was evaluated. A health-based drinking water concentration was developed using end points for toxicity identified by U.S. Environmental Protection Agency (USEPA) (*29*). Both the exposure assessment and health-based water concentration were based on the observed relationship between the concentration of PFOA in drinking water and serum in humans (*16*).

Experimental Section

Sample Site Selection. For the 2006 occurrence study, 36 samples collected by the New Jersey Department of Environmental Protection (NJDEP), including 29 from 23 PWS, one duplicate sample, six field blanks, and one trip blank, were analyzed for PFOA. The study included systems supplied by groundwater and surface water.

The systems chosen included seven with surface water intakes within 10 miles, or with public wells within 1 mile, of five facilities where PFOA or related chemicals may have been present. Four additional systems with a history of organic contamination were included, since these systems are thought to be impacted by releases from industrial and commercial activities, increasing the likelihood of PFOA detection (*30*). One groundwater and one surface water system with no history of organic contamination were

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10.1021/es900301s CCC: $40.75
Published on Web 05/08/2009

TABLE 1. PFOA in NJ PWS Sampled by NJDEP, 2006[a]

site no.	public water system ID number	source water	raw/ finished	PFOA (μg/L)
1	NJ2119001	GW, unconfined	Raw	ND[b]
2-W1	NJ0217001, Well 1	GW, unconfined	raw	0.026
2-W2	NJ0217001, Well 2	GW, unconfined	raw	0.033
3	NJ0221001	GW, unconfined	raw	0.033
4	NJ1604001	GW, unconfined	raw	0.029
5	NJ1107002	GW, unconfined	raw	0.007
6	NJ0424001	GW, unconfined	raw	ND
7	NJ0119002	GW, unconfined	raw	NQ[c]
8	NJ0717001	GW, unconfined	raw	0.021
9	NJ1434001	GW, unconfined	raw	0.008
10	NJ0614003	GW, unconfined	raw	ND
11R	NJ1435002	GW, unconfined	raw	0.006
11F	NJ1435002	GW, unconfined	finished	0.006
12[d]	NJ1007002	GW, unconfined	finished	0.005
13GW[e]	NJ1712001	GW, semiconfined	raw	0.027/0.025[f]
14	NJ1316001	GW, confined	raw	ND
15	NJ0514001	GW, confined	finished	ND
16	NJ1613001	SW	raw	0.008
13SW[e]	NJ1712001	SW	raw	0.010
17	NJ1219001	SW	raw	0.014
18	NJ1915001	SW	finished	NQ
19R	NJ0327001	SW	raw	NQ
19F	NJ0327001	SW	finished	NQ
20R	NJ1605002	SW	raw	0.026
20F	NJ1605002	SW	finished	0.027
21R	NJ2013001	SW	raw	0.035
21F	NJ2013001	SW	finished	0.039
22	NJ1352005	SW, reservoir	raw	0.011
23	NJ0238001	SW, reservoir	raw	0.021

[a] GW, ground water; SW, surface water. [b] ND, not detected. [c] NQ, detected below RL. [d] There is no history of organic contamination at these PWS. [e] This PWS has both a groundwater and a surface water source. [f] Laboratory duplicate.

selected for comparison (*30*). Other sites were chosen to expand the geographic extent of the sampling. Both raw and finished water samples were collected at three surface water and one groundwater system.

In 2007–2008, additional sampling was conducted by NJ PWS. Samples (201) were collected from points of entry (POEs) into the distribution system, individual wells, and surface water intakes at 18 systems, including 12 with detectable levels of PFOA in 2006, and six not sampled in 2006.

Sampling Procedure. Sample collection was performed by NJDEP personnel, following the standard operating procedure for the analytical method (*31*). A single unfiltered 250 mL grab sample was collected from designated sampling locations used for other monitoring purposes.

Six field blanks were prepared by pouring distilled water into collection bottles at sites where the greatest and least possibility of contamination was expected. The trip blank containing distilled water was prepared by the analytical laboratory, shipped to NJDEP personnel, and returned to the laboratory unopened with that day's other samples. A duplicate sample was collected at one site (Table 1).

Procedures for sampling conducted by NJ systems in 2007–2008 conformed to relevant NJDEP and USEPA regulations, with analysis performed by several NJDEP certified laboratories.

Analytical Method. The 2006 samples were analyzed for PFOA by Test America, Denver, CO using liquid chromatography and tandem mass spectrometry (LC/MS/MS) (Micromass Ultima MS/MS or Waters Micromass Quattro Premier tandem mass spectrometer) (*31*). An isotope dilution technique using a 13C labeled PFOA analog is used to quantify PFOA. The PFOA parent ion (m/z = 413 amu) and two daughter ions (m/z = 369 and 219 amu) are used for qualitative identification. This approach provides low detection limits and a high level of qualitative certainty.

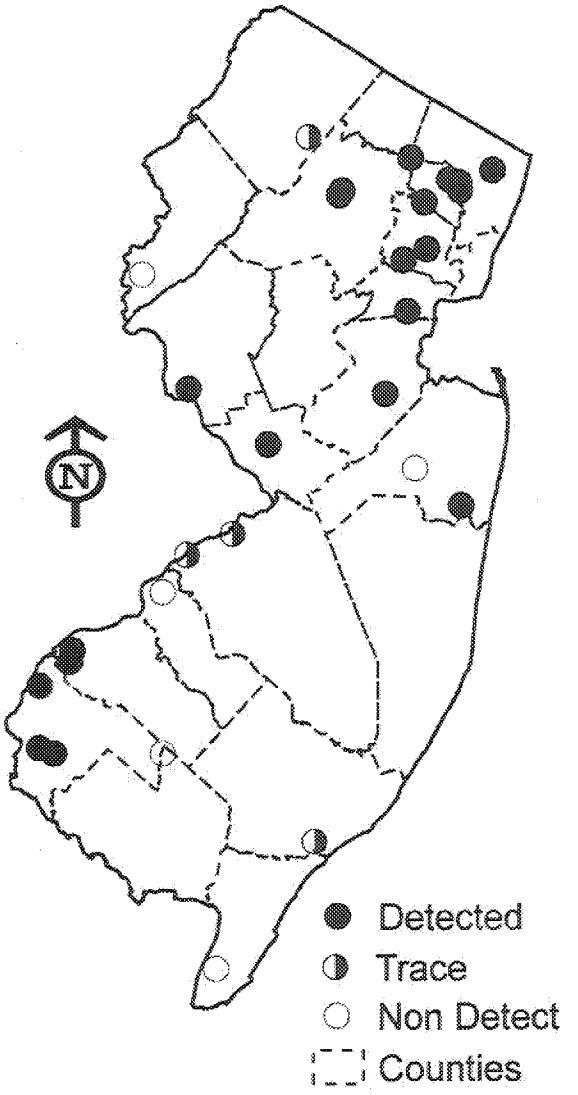

FIGURE 1. Locations of NJ PWS sampled in 2006 PFOA occurrence study.

The laboratory's reporting limt (RL) for this study was 0.004 μg/L. Detections below the RL are reported as not quantifiable (NQ).

The 2007–2008 samples were analyzed by several laboratories certified by NJDEP using the LC/MS/MS technique. Samples were generally collected and analyzed quarterly. Reporting values differ among laboratories and ranged from 0.01 to 0.015 μg/L.

Results and Discussion

2006 Study of Occurrence of PFOA in NJ PWS. PFOA was detected at or above the RL in 20 (69%) of the 29 samples, and in four additional samples below the RL (Table 1, Figure 1). Of the 23 PWS in this study, 15 (65%) had detections at or above the RL, and three additional systems had detections below the RL. PFOA was detected in 9 of 12 (75%) raw groundwater samples from unconfined or semiconfined aquifers, but was not detected in the two raw (e.g., untreated) groundwater samples from confined aquifers. All three samples of finished (e.g., treated) groundwater from unconfined aquifers had detectable levels of PFOA. Seven of

TABLE 2. NJ PWS with PFOA Detections ≥0.04 μg/L in Data Submitted to NJDEP, 2007–2008[a]

site no.	PWSID	source water	type	number of samples	average (μg/L)	range (μg/L)
8A	NJ0717001	GW, unconfined	POE	4	0.068	0.058–0.084
8B	NJ0717001	GW, unconfined	POE	4	0.069	0.063–0.072
24	NJ0809002	GW, unconfined	POE	3	0.050	0.018–0.069
25A	NJ1707001	GW,unconfined	Well 1	5	0.083	0.062–0.1
25B	NJ1707001	GW, unconfined	Well 2	6	0.078	0.055–0.14
25C	NJ1707001	GW, unconfined	POE	6	0.079	0.053–0.10
21	NJ2013001	SW	POE	1	0.040	0.040
3	NJ0221001	GW, unconfined	POE	4	0.034	0.029–0.048

[a] GW, ground water; SW, surface water.

the eight raw surface water samples and two of the four finished surface water samples had detectable levels of PFOA. There was no apparent difference between raw and finished water collected at the same system. PFOA was not detected above the health-based concentration (see below) of 0.04 μg/L in this study. PFOA was not detected in the six field blanks or the one trip blank. Additional details are provided in an NJDEP report (*28*).

Additional PFOA Data from NJ PWS. In 2006, PFOA data were submitted to NJDEP from two PWS with wells located near a facility that used PFOA in manufacturing processes and processed waste containing PFOA. These samples were analyzed by Axys Analytical Services, Sidney, Canada, and Exygen Research, State College, PA. At one of these systems (NJ1707001, site no. 25), PFOA was detected at up to 0.123 and 0.19 μg/L in shallow, unconfined wells from two different wellfields, but was not detected in deep unconfined wells from these wellfields. At the other system (NJ1708001, site no. 26), PFOA was detected in one of eight raw groundwater samples at 0.0176 and 0.0179 μg/L, and in finished water up to 0.0081 μg/L (*28*).

In 2007–2008, 201 samples collected by 18 PWS, including 12 sampled in the 2006 study, were analyzed for PFOA. Samples were collected from one or more POE at each system, with one to six samples for each POE, as well as from individual wells and surface water intakes. PFOA concentrations ranged from nondetectable (<0.01 μg/L) to 0.14 μg/L. PFOA was detected at or above the health-based concentration (see below) of 0.04 μg/L in at least one sample from five systems (Table 2), including one not sampled in 2006. Yearly average concentrations (average results from four consecutive quarters) exceeded the health-based concentration for four POE from three different systems.

Potential Contribution of PFOA at Concentrations Found in NJ Drinking Water to PFOA in Serum. A median ratio of approximately 1:100 was observed between the concentration of PFOA in drinking water and serum in Little Hocking, Ohio (*16*). In this community, drinking water had been contaminated by a nearby industrial facility, with an average concentration of 3.55 μg/L in 2002–2005. The median PFOA serum concentration in 282 individuals tested in 2004–2006 was 371 μg/L, with occupationally exposed individuals excluded. This ratio is based on those six years and older, while a higher ratio was observed for younger children (*16*). The ratio was based on data from individuals who had resided in Little Hocking for at least two years and was not related to years of residence. If a similar relationship is valid at lower drinking water concentrations, such as those detected in NJ (Tables 1 and 2), then such concentrations may contribute substantially to total exposure to PFOA.

Data are available on both the range of historic drinking water concentrations (*32*) and the serum levels of PFOA in samples taken in 2005–2006 (*33*) in five Ohio and West Virginia water districts with lower PFOA concentrations than Little Hocking. The median serum level in each of these districts (Table 3) is higher than the U.S. median of 4 μg/L

TABLE 3. PFOA Levels in Drinking Water and Serum in Communities in Ohio and West Virginia

water district	PFOA levels reported by water district (μg/L) (*32*)	median serum PFOA level (μg/L) (*33*)
Little Hocking, OH	1.7–4.3	224
Lubeck, WV	0.4–3.9	70
Tuppers Plains, OH	0.25–0.37	35
City of Belpre, OH	0.08–0.13	37
Mason County, WV	0.06–0.1	12
Village of Pomeroy, OH	0.06–0.07	12

(*2*). The range of PFOA levels in these districts may include results from multiple POEs, and the number of people served by each POE, as well as the variation of concentration over time, are not known. Therefore, the mean or median drinking water concentrations in these districts cannot be accurately estimated from the range of concentrations. For this reason, the median ratio of drinking water to serum concentrations for these districts cannot be reliably determined, as was done for Little Hocking (*16*). However, it can be seen that the median PFOA serum concentration increases with increasing PFOA concentration in the drinking water.

Village of Pomeroy had the lowest PFOA concentration (0.06–0.07 μg/L), about 50-fold lower than in Little Hocking. Since this range is narrow, the average can be reliably estimated as 0.065 μg/L. Based on this estimate, the average ratio of PFOA in serum to drinking water in this district is 185:1.

For lower drinking water concentrations, nonwater sources are likely to contribute a greater proportion of the PFOA in the blood than in those using highly contaminated water. To find a lower bound on the ratio of serum to water PFOA concentrations, it can be assumed that none of the U.S. background serum concentration of about 4 μg/L results from drinking water. If this serum concentration of 4 μg/L is subtracted from the median serum concentration for Village of Pomeroy (12 μg/L), the ratio of the remaining serum concentration (8 μg/L) to the drinking water concentration (0.065 μg/L) is 123:1. Therefore, PFOA appears to concentrate in serum of people exposed to lower drinking water concentrations in a similar ratio to that reported in a highly exposed community (*16*).

It should be noted that serum levels for individuals with occupational exposure (2% current, 3% former) (*33*) were not excluded from the data shown in Table 3. However, since the number of subjects in each district is large, and the serum concentrations are medians, rather than means, it is unlikely that the overall trend would change if occupationally exposed individuals were excluded.

This observed serum/drinking water ratio of approximately 100:1 is in agreement with a one-compartment model (*34*) which predicts that ingestion of 0.0017 μg/kg/day would result in serum levels of 13 μg/L in males and 8 μg/L in

females, or a mean of 10.5 μg/L. Assuming a drinking water intake of 0.017 L/kg/day (*35*), a dose of 0.0017 μg/kg/day would result from a water concentration of 0.1 μg/L. The ratio between a serum concentration of 10.5 μg/L and this water concentration of 0.1 μg/L is 105:1, identical to the median ratio reported in Little Hocking (*16*).

These results suggest that PFOA in drinking water at concentrations such as those found in NJ PWS can substantially contribute to total exposure to PFOA. For example, PFOA was found at ≥0.01 μg/L in 13 of 29 samples in the 2006 study (Table 1). Based on the 100:1 ratio, a drinking water concentration of 0.01 μg/L is estimated to contribute about 1 μg/L to PFOA in serum, or about 25% of the 4 μg/L median serum level in the general population.

Development of a Health-Based Drinking Water Concentration for PFOA. The draft risk assessment for PFOA developed by USEPA (*29*), which identified toxicological end points in experimental animals, was used as the starting point for development of a health-based drinking water concentration protective for lifetime exposure. The goal of the USEPA risk assessment (*29*) was to evaluate the significance of exposure in the general population. Because the half-life of PFOA is much longer in humans (several years) than in the animals studied (2−4 h to 30 days) (*5*, *29*), a given external dose (e.g., administered dose in units of mg/kg/day) results in a much greater internal dose (as indicated by serum level) in humans than in animals. Therefore, comparisons between effect levels in animal studies and human exposures were made on the basis of serum levels rather than external dose (*29*).

USEPA (*29*) compared serum levels of PFOA at the No Observed Adverse Effect Levels (NOAELs) or Lowest Observed Adverse Effect Levels (LOAELs) from animal studies to serum levels of PFOA in the general human population to develop margins of exposure for noncancer end points. Additionally, USEPA (*29*) classified PFOA as having "suggestive evidence of carcinogenic potential", whereas the USEPA Science Advisory Board (*36*) disagreed and recommended a classification of "likely to be carcinogenic to humans". The blood concentrations at the NOAELs and LOAELs for noncancer end points (*29*), as well as for the data used for cancer risk assessment (*37*), are shown in Table 4.

USEPA (*29*) did not develop a Reference Dose (RfD) or cancer slope factor for PFOA, nor did they address the relationship between the external dose and the human serum level. Information on this relationship is valuable for development of a health-based drinking water concentration. To develop a health-based drinking water concentration for PFOA, we derived target human serum levels by applying standard uncertainty factors (UFs) for RfD development (*38*) to the measured or modeled serum levels identified (*29*, *39*) as NOAELs or LOAELs for noncancer end points (Table 4).

The UF of 10 for interspecies extrapolation typically includes two factors of 3 each for toxicokinetic and toxicodynamic differences between humans and animals (*38*). Since the health-based drinking water concentrations are based on comparison of serum levels in animals and humans, the question arose as to whether comparison on this basis fully addresses interspecies toxicokinetic differences, and whether an interspecies UF of 3 rather than 10 is thus appropriate. The USEPA Science Advisory Board (*36*) believed that overall uncertainty about the interspecies differences in PFOA toxicity was not sufficiently reduced by comparison on the basis of serum levels to justify modifying the default interspecies UF. Therefore, the standard interspecies UF of 10 was used.

For the cancer end point, the serum level resulting in a 10^{-6} risk level was estimated by linear extrapolation from the serum level in animals at a dose resulting in an approximate 10% tumor incidence (Table 4 (*37*)). Linear extrapolation is recommended by USEPA (*40*) as a default approach when the mode of action for carcinogenicity is unknown.

In developing health-based drinking water values for noncancer end points, a relative source contribution (RSC) is applied to account for nondrinking water exposures to the contaminant (*41*, *42*). The default value for this factor is 20% (e.g., nondrinking water sources are assumed to provide 80% of exposure) when the relative contributions of drinking water versus nondrinking water sources are not fully characterized, as is the case for PFOA. Therefore, an RSC of 20% was applied to the target human serum levels for noncancer end points to derive the serum concentrations that are the target contribution to the human serum levels from drinking water (Table 4). No RSC is used for the cancer end point, as the target human serum concentration is based on the 10^{-6} risk level from drinking water exposure only.

As discussed above, the relationship between external dose and serum level was used for development of a health-based drinking water concentration for PFOA. The ratio of 100:1 between the concentration of PFOA in serum and in drinking water which was reported for a high drinking water concentration (*16*) also appears to be valid at lower concentrations relevant to this analysis (Table 3). The health-based drinking water concentration for each end point was derived using the 100:1 ratio from the target human serum concentration contributed by drinking water for that end point (Table 4). As this approach is based on the observed relationship between serum and drinking water concentrations, assumptions for body weight and volume of water ingested daily are not required.

The range of health-based drinking water concentrations for the seven end points assessed is 0.04−0.26 μg/L, and several of the concentrations are very similar: 0.04, 0.05, 0.06, 0.07, and 0.08 μg/L (Table 4). The most sensitive end points, resulting in the lowest drinking water concentration of 0.04 μg/L, were decreased body weight and hematological effects in the adult female rat. Cancer was not the most sensitive end point, as the drinking water concentration based on the 10^{-6} cancer risk level is 0.06 μg/L. Therefore, the recommended health-based drinking water concentration for PFOA is 0.04 μg/L.

Both the USEPA Site Specific Action Level for PFOA in drinking water in West Virginia and Ohio (*43*), and the Minnesota Department of Health's (MNDOH) Health Based Value (*44*) for PFOA in groundwater are 0.5 μg/L. These assessments are based on a 6 month (subchronic) study in male cynomolgus monkeys (Table 4), and use the ratio of half-lives for PFOA to extrapolate between animals and humans, rather than the 100:1 ratio between serum and drinking water used in Table 4. Based on pharmacokinetic principles, both approaches should give the same result if the parameters and assumptions used are correct. The drinking water concentration derived in Table 4 for the same study and end point used by USEPA (*43*) and MNDOH (*44*) is 0.05 μg/L. The 10-fold difference arises only because the drinking water concentrations developed in Table 4 include an UF for extrapolation from subchronic to chronic exposure, while the USEPA and MNDOH risk assessments do not. Aside from the 10-fold difference, which is explained by the use of the UF for duration of exposure, the approach used in Table 4 and the approaches used by USEPA and MNDOH give identical results, providing further strength for the use of the 100:1 ratio in developing a health-based drinking water concentration for PFOA.

Recent Human and Animal Data Not Considered in Development of a Health-Based Drinking Water Concentration. The health-based drinking water concentration of 0.04 μg/L considered only toxicological end points identified

TABLE 4. Derivation of Health-Based Drinking Water Concentrations for PFOA from End Points in Animal Studies (*29*)

species	key study (*29*)	end point (*29*)	NOAEL or LOAEL (*29*)	animal serum level (μg/L) at LOAEL or NOAEL (*29*)	uncertainty factor	target human serum level[a] (μg/L)	target contribution to human serum from drinking water[b] (μg/L)	health-based drinking water concentration[c] (μg/L)
adult female rat	chronic diet	↓ body weight, hematology	NOAEL 1.6 mg/kg/day (30 ppm)	1800 (based on modeled AUC)	100 (10 intraspecies, 10 interspecies)	18	4	0.04
adult male rat	two-generation reproductive, gavage	↓ body weight, ↑ liver and kidney weight in F1 generation	LOAEL 1 mg/kg/day	42 000 (USEPA model)	1000 (10 intraspecies, 10 interspecies, 10 LOAEL to NOAEL)	42	8	0.08
nonhuman primate	subchronic male cynomolgus monkey, capsule	increased liver weight and possible mortality	LOAEL 3 mg/kg/day	77 000 (measured)	3000 (10 intraspecies, 3 interspecies, 10 subchronic to chronic, 10 LOAEL to NOAEL)	26	5	0.05
pregnant female rat	two-generation reproductive, gavage	↓ body weight in male F1 pups during postweaning	NOAEL 3 mg/kg/day	3500 (based on modeled AUC)	100 (10 intraspecies, 10 interspecies)	35	7	0.07
male rat pups, postweaning	two-generation reproductive, gavage	↓ body weight in male F1 pups during postweaning	NOAEL 3 mg/kg/day	8400 (based on modeled AUC at week 4)	100 (10 intraspecies, 10 interspecies)	84	17	0.17
female rat pups, postweaning	two-generation reproductive, gavage	↓ body weight in female F1 pups during postweaning	NOAEL 10 mg/kg/day	13 000 (based on modeled AUC at week 7)	100 (10 intraspecies, 10 interspecies)	130	26	0.26
male rats (tumor) (*37*)	chronic diet	Leydig cell, pancreatic, and liver tumors	13.6 mg/kg/day (300 ppm) (~10% tumor incidence) (LOAEL or NOAEL not applicable)	572 000 μg/L (USEPA model)	not applicable, target human serum level is based on linear extrapolation from 10^{-1} tumor incidence to 10^{-6} incidence	5.7	5.7	0.06[d]

[a] Target human serum level is derived by application of uncertainty factors to animal serum level at NOAEL or LOAEL. [b] Target contribution to human serum from drinking water is derived by applying a relative source contribution factor of 20% (to account for nondrinking water sources of exposure) to target human serum level. [c] Health-based drinking water concentration assumes a 100:1 ratio between PFOA concentrations in serum and drinking water (*16*). [d] Note: 20% relative source contribution factor was not used for cancer endpoint.

by USEPA (29). Additional data from human and animal studies not considered by USEPA (29) have since become available.

The developmental studies considered by USEPA (29) were conducted in rats. The rat is not an appropriate model for evaluating potential human developmental effects of PFOA because its half-life in the female rat is very short (2−4 h) (5). In the two-generation rat study considered by USEPA (29) in which PFOA was administered as a bolus dose, blood levels did not reach steady state and exposure to the developing fetuses was not continuous. The mouse is more appropriate for developmental studies of PFOA, since the half-life in female mice is longer (17 days) (5), and PFOA levels reach steady state, with continuous exposure to the fetuses. Recent mouse developmental studies (5, 45−48) show significant effects not seen in the rat, including full litter resorptions, postnatal mortality, decreased birth weight, delayed growth and development, effects on mammary gland development, increased pup liver weight, structural changes in the uterus, and metabolic effects in adulthood after prenatal exposures.

USEPA (49) has recently (January 2009) developed a Provisional Short-term Health Advisory for PFOA in drinking water of 0.4 μg/L, based on increased maternal liver weight after administration of PFOA for 17 days (45). Applying a standard UF of 10 for subchronic to chronic exposure to this value would result in a drinking water concentration of 0.04 μg/L, identical to the lifetime health-based guidance developed here. However, exposure for 17 days is insufficient to be considered subchronic (50), and therefore may not be appropriate for extrapolation to a chronic risk assessment based on a systemic effect such as increased liver weight. Additionally, other studies of similar or shorter duration not considered by USEPA (49) show effects in mice at doses below those used in the study selected by USEPA (45). These effects include increased liver weight in dosed adults (51), and increased pup liver weight (46), metabolic effects in adulthood (47), and structural changes in the uterus (48) following prenatal exposure. Evaluation of these studies could result in a short-term health-based concentration below 0.4 μg/L.

Preliminary data are available from the C8 Health Study, a study of approximately 70 000 people in Ohio and West Virginia exposed to PFOA in drinking water at 0.05 μg/L or above (11, 33). This study is unique because serum levels were measured, so that effects may be correlated with internal dose rather than with a surrogate such as drinking water concentration for this very large study group. The median serum levels in the first and second deciles, 6 and 9.8 μg/L (11) are within the range prevalent in the U.S. general population, where, for 2003−2004, the 75th and 95th percentile levels were 5.8 and 9.8 μg/L (2). Increased cholesterol and other lipids were associated with serum PFOA levels, after adjustment for age, gender, body mass index, and other factors (12). In the cholesterol study (12), the median PFOA serum level was 27 μg/L, and the risk of high cholesterol increased in each quartile of exposure with a 40−50% increase in the top quartile compared to the lowest quartile. Similarly, serum PFOA was significantly associated with increased uric acid levels (52) and changes in several indicators of inflammatory and immune response (53) in this population. Additionally, preliminary data suggest an association between PFOA serum levels and several other clinical parameters measured in blood, including liver enzymes (11). It should be noted that these studies are ongoing and the results are currently undergoing peer review.

The health-based drinking water concentrations developed in this paper (Table 4) are intended to protect against adverse effects from a lifetime of exposure. They are based on target human serum levels developed from animal data through a conservative approach using standard UFs for RfD development. However, recent data suggest that biological effects may occur in humans in the range of the target serum levels presented in Table 4. The lowest target serum level derived from animal studies (18 μg/L) falls within the second quartile of the C8 Health Study (12), where associations with elevated cholesterol and uric acid, and changes in immune system function, were seen (12, 33, 52, 53). Additionally, associations with effects on growth of infants (6−8), increased time to pregnancy (54), and decreased normal sperm count (55) were reported in humans at serum levels below the target human serum levels in Table 4, although other studies (9, 10) did not show effects on infant growth.

In conclusion, PFOA was commonly detected in raw and finished water from NJ PWS using both surface and groundwater sources. Based on the relationship between the PFOA concentrations in drinking water and serum in humans, drinking water concentrations such as those detected in NJ (e.g., 0.01 μg/L) may contribute substantially to total exposure to PFOA. A health-based drinking water concentration of 0.04 μg/L was developed based on effects in animal studies. Recent animal and human studies provide additional information on exposure to and effects of PFOA. While PFOA in most NJ PWS was below the health-based concentration, several New Jersey PWS exceeded this concentration.

Acknowledgments

The occurrence study was conducted through the cooperative efforts of the staff of the NJ Department of Environmental Protection Bureau of Safe Drinking Water, Office of Quality Assurance, and Division of Science, Research and Technology (DSRT), including Edward Apalinski, John Berchtold, Linda Bonnette, Alan Dillon, Marc Ferko, Karen Fell, Barker Hamill, Dr. Eileen Murphy, Michele Putnam, and Dr. Bernie Wilk. We thank Gail Carter of DSRT for creating the map, Dr. Thomas Atherholt of DSRT for helpful comments, and Dr. Alan Stern of DSRT and Dr. Perry Cohn of the NJ Department of Health and Senior Services for their earlier review of the basis for the health-based drinking water concentration. Finally, we especially thank Dr. Eileen Murphy, Director, DSRT, for her enthusiastic support of this work. The views expressed are those of the authors and do not necessarily represent those of the New Jersey Department of Environmental Protection.

Note Added after ASAP Publication

There was an error in the range column of Table 2 in the version of this paper that published ASAP May 8, 2009; the corrected version published ASAP May 12, 2009.

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ES900301S